

ORIGINAL ARTICLE

Opportunities and Challenges in Establishing a Cohort Study: An Example From Cleft Lip/Palate Research in the United Kingdom

Nicola Marie Stock, M.Sc., Kerry Humphries, M.Sc., Beate St Pourcain, Ph.D., Maggie Bailey, B.A., Martin Persson, Ph.D., Karen M. Ho, B.Sc., Susan Ring, Ph.D., Cathy Marsh, R.S.C.N., Liz Albery, M.Phil., Nichola Rumsey, Ph.D., Jonathan Sandy, Ph.D.

Background: Cleft lip and/or palate (CL/P) is one of the most common birth conditions in the world, but little is known about its causes. Professional opinion remains divided as to which treatments may be the most beneficial for patients with CL/P, and the factors that contribute to psychological adjustment are poorly understood. The use of different methodological approaches and tools plays a key role in hampering efforts to address discrepancies within the evidence base. A new UK-wide program of research, The Cleft Collective, was established to combat many of these methodological challenges and to address some of the key research questions important to all CL/P stakeholders.

Objective: To describe the establishment of CL/P cohort studies in the United Kingdom and to consider the many opportunities this resource will generate.

Results: To date, protocols have been developed and implemented within most UK cleft teams. Biological samples, environmental information, and data pertaining to parental psychological well-being and child development are being collected successfully. Recruitment is currently on track to meet the ambitious target of approximately 9800 individuals from just more than 3000 families.

Conclusions: The Cleft Collective cohort studies represent a significant step forward for research in the field of CL/P. The data collected will form a comprehensive resource of information about individuals with CL/P and their families. This resource will provide the basis for many future projects and collaborations, both in the United Kingdom and around the world.

KEY WORDS: *cause, cleft, cohort study, environment, gene, measurement, psychological adjustment, treatment*

A cleft in the lip and/or the palate (CL/P) is one of the most common birth conditions. However, as yet, understanding about the causes of this congenital anomaly and the impact on those affected is limited. Progress is hampered by methodological challenges, including heterogeneity in cleft types, small sample sizes, incomplete data

relating to treatment, and a lack of consistency in the outcomes measured. This article highlights efforts to address these methodological shortcomings through the initiation of UK-wide cohort studies. The opportunities and challenges posed in this process are discussed.

Identifying the Causes of Cleft

It is now widely acknowledged that cleft has a multifactorial etiology, comprising both genetic and environmental factors (Mossey et al., 2009). It is estimated that in 70% of all cases of CL±P and in 50% of cases of cleft palate alone, the cleft occurs in isolation without an association to any known syndrome (“nonsyndromic”; Dixon et al., 2011). The remaining forms of cleft are thought to relate to a wide range of syndromes, including more than 500 Mendelian syndromes and those cases that have chromosomal or teratogenic influences (Dixon et al., 2011). In recent years, there has been significant progress in the identification of causative genetic mutations underlying syndromic forms of CL/P. Although recent genome-

Ms. Stock is Healing Foundation Research Fellow, Dr. Persson is Senior Research Fellow, and Dr. Rumsey is VTCT Professor of Appearance Research and Co-Director, Centre for Appearance Research, University of the West of England, Bristol, United Kingdom. Ms. Humphries is Project Manager, Dr. St Pourcain is Lecturer in Genetic Epidemiology, Ms. Bailey is Project Coordinator, Ms. Ho is Research Assistant, Dr. Ring is Head of Laboratories, and Dr. Sandy is Professor of Orthodontics, Faculty of Medicine and Dentistry, University of Bristol, United Kingdom. Ms. Marsh is Lead Specialist Cleft Nurse and Ms. Albery is Clinical Director/Lead Speech and Language Therapist, South West Cleft Service, University Hospitals Bristol NHS Foundation Trust, United Kingdom.

Submitted November 2014; Revised March 2015; Accepted March 2015.

Address correspondence to: Ms. Nicola Marie Stock, Centre for Appearance Research, University of the West of England, Coldharbour Lane, Bristol, BS16 1QY, United Kingdom. Email Nicola2.Stock@uwe.ac.uk.

DOI: 10.1597/14-306

wide association studies have made progress in understanding the role of common genetic variation within nonsyndromic forms of CL/P (Birnbaum et al., 2009; Grant et al., 2009; Mangold et al., 2010; Beaty et al., 2010; Ludwig et al., 2012), our understanding of this has been much slower. This is largely because of the genetic heterogeneity, the sporadic nature of the anomaly, the lack of large data sets, and the costs of investigating whole genomes. Large studies are needed to capitalize on recent innovations in phenotyping and information from syndromic forms of CL/P and to investigate the role of rare genetic variation (through, for example, next-generation sequencing studies).

Possible environmental risk factors of facial clefting include maternal smoking and maternal alcohol intake (Dixon et al., 2011). More importantly, genetic risk may be moderated by environmental factors (Wu et al., 2010; Beaty et al., 2011; Dixon et al., 2011), underlining the need to increase our understanding of gene-environment interactions. Potential environmental moderators include nutritional factors, such as folate deficiency, as well as drug use (such as phenytoin and cocaine), hyperthermia, stress, maternal obesity, ionizing radiation, and infection (see Dixon et al., 2011). To date, there have been very few attempts to investigate the interplay of genetic and pre-/perinatal environmental influences in nonsyndromic CL/P at a genome-wide level (Stanier and Moore, 2004; Beaty et al., 2011). Although information on these risk factors is usually obtained retrospectively (e.g., within case collections), it is likely that birth cohorts will ascertain more reliable information because of the more accurate recall of recent information at the time point of recruitment.

While a better understanding of the genetic components involved in clefting would allow for clearer information regarding causes and recurrence risks to be given to families, malleable identification of environmental risks would afford some short-term opportunities for prevention.

Impacts of Cleft

In resource-rich countries, CL/P is not normally a life-threatening condition. Nonetheless, the burden of care for the patient and their family can be substantial. As well as feeding difficulties, hearing impairments, dental problems, and speech and language impediments, patients may undergo several surgical procedures to repair the cleft and its associated malformations. This multidisciplinary level of care is likely to continue throughout the patient's childhood and often into adulthood. Despite modern surgical advances and recent improvements in service provision in the United Kingdom (Sandy et al., 1998, 2012), the evidence base

for optimal treatments remains very weak, and the true impact of care is still largely unknown.

As well as the requirement to engage with multidisciplinary care over many years, patients and their families may experience a number of psychological and social challenges. Following a diagnosis of CL/P in their child, parents often express feelings of guilt, grief, and concern over their child's future (Nelson et al., 2012). For the child, looking and/or sounding different to their peers may interfere with social interaction and invite some degree of teasing or bullying (Hearst, 2007). Difficulties surrounding emancipation from the family unit and the initiation of intimate relationships may also be problematic (Noar et al., 1991; Danino et al., 2005). For prospective parents, decision making around starting or expanding a family may evoke distress due to the recurrence risk (Stock and Rumsey, in press). The full spectrum of cognitive, behavioral, and emotional challenges remains uncharted, and ways of optimizing educational and vocational outcomes for individuals with CL/P need to be investigated (Persson et al., 2012; Richman et al., 2012; Rumsey and Stock, 2013). Factors that contribute to psychological distress and resilience are still poorly understood (Hunt et al., 2005), and research to establish the optimal type and timing of interventions to aid psychosocial adjustment to CL/P is an urgent priority (Petit-Zeman and Cowan, 2013; Norman et al., 2015). A large-sample prospective study has the potential to generate data to address these pressing questions.

Addressing Current Methodological Challenges

As outlined above, advances in understanding in this field have been hampered by small sample sizes, the heterogeneity in types of clefting, and a lack of consensus in approaches to methodology and measurement. The problem of recruiting sufficiently large numbers of participants to research studies in this field is widely recognized but difficult to overcome. In an attempt to ease recruitment challenges and to reduce heterogeneity, previous studies have in the main focused on specific patient groups (e.g., children with unilateral cleft lip and palate only), resulting in a paucity of knowledge about those patients who are excluded (Dixon et al., 2011; Feragen et al., 2014). Although some comorbidities may be immediately obvious at birth, others manifest much later, yet all may contribute to long-term outcomes, such as educational achievement and mental and physical well-being (see Feragen and Stock, 2014). To address these questions and to make precise estimates of either the incidence of an outcome or the relative risk of an outcome based on exposure, prospective investigation is needed (Levin, 2006).

Another limitation of existing research is that it is often carried out in relation to a single discipline (e.g., orthodontics). Despite global calls for a multidisciplinary and holistic approach to care, little is known about how different aspects of care overlap, interact, and affect the patient and family (for example, psychological adjustment and speech and language development). Similarly, data have usually been collected from patients attending a single treatment site or collected inconsistently between centers, preventing the opportunity for meaningful comparisons across locations and patient populations.

In response to current methodological limitations, multidisciplinary and multicenter approaches to audit and research are necessary. Longitudinal research is needed to shed light on the differing needs of patients and families over time. In addition, there is a need to include all patients in samples, irrespective of diagnosis or the presence of an additional condition or syndrome. To address many of the current gaps in knowledge, large, prospective cohort studies with access to genetic material are critical (Dixon et al., 2011). The centralization of care for those affected by CL/P and their families (Sandy et al., 1998, 2012) has placed the United Kingdom in the unique position to establish one such national study.

To the authors' knowledge, although some cohort studies currently exist, the genetic information collected is not easily accessible, and environmental information is not readily available. In addition, few CL/P case-control studies involving a representative sample have been conducted (Ludwig et al., 2012). The Cleft Collective cohort studies will accumulate genetic information from the biological mother, father, affected child, and a limited number of siblings, as well as environmental information relating to before, during, and after pregnancy. In line with a holistic approach, additional information will be collected in relation to each of the key disciplines, including psychological well-being, speech and language development, surgical treatment, orthodontics, audiology, nursing, and three-dimensional (3D) imaging. The cohort studies will also ask permission from participants to link into medical and educational records, as well as cleft-specific national databases. The cohort studies will build on and complement the data collected through past and current outcomes studies in Europe (Eurocleft; see Shaw et al., 2001) and the United States (Americleft; see Long et al., 2011).

The aim of the present article is to describe the establishment of a CL/P cohort study in the United Kingdom and to consider the opportunities this resource will generate, both in the United Kingdom and around the world.

METHOD

Getting Started

Feasibility

Following the centralization of cleft services in the United Kingdom, the Craniofacial Society of Great Britain and Ireland (CFSGBI) recognized the potential for a significant increase in research activity. Despite this, the number of studies taking place at that time remained limited, and no research priorities for the field had been agreed. In response, the CFSGBI funded a succession of workshops for clinicians and researchers to discuss how to best move cleft research forward. It was here that the idea of a "gene bank" and cohort study was suggested. Before progressing any further, it was necessary to ascertain whether such a study would be feasible. Researchers from the University of Bristol conducted a series of qualitative interviews and focus groups with parents of children born with CL/P to identify the factors that may contribute to participation in a CL/P gene bank and how this could be facilitated (Williams et al., 2012). The study confirmed the value and importance of establishing this type of research, while also highlighting a number of sensitive issues that required additional consideration.

Patient and Public Involvement

To explore this further, a number of patient and public involvement (PPI) workshops were held. Several parents of children with CL/P attended these workshops, as well as key representative organizations such as the Cleft Lip and Palate Association (CLAPA) and the James Lind Alliance. In addition to some basic training on involvement in research, attendees were provided with an overview of the research proposal and asked to provide feedback regarding the draft protocols and materials. Key issues such as the timing and method of approaching potential participants, the importance of providing clear information regarding how biological samples would be collected and stored, and how the research findings would be fed back to participants were discussed.

Researcher and Clinician Involvement

Next, a 1-day workshop for clinicians and researchers currently working within CL/P and related fields was conducted. Feedback was collected from various health professionals throughout the day in relation to the practical challenges of integrating the research protocol alongside clinical practice. It became clear that the proposed research was necessary and would yield

findings that would be highly valued by all stakeholders. Nonetheless, the challenges involved in initiating and maintaining such a project were considerable.

Funding

The first challenge to overcome was the need to secure funding for the project. The UK-based charity The Healing Foundation had been involved and interested since the initial discussions were held, and following a substantial application to the committee, funding was agreed in the form of charitable donations. It was established that this funding would support the project for 5 years from May 2012 and would be divided between a Cleft Clinical Trials Unit based in Manchester and Cleft Cohort Studies based in Bristol. The associated universities and hospital trusts in Manchester and Bristol also agreed to provide matched funding, with an overall funding envelope of 10 million pounds. The research program was to operate under the title of The Cleft Collective and represented a significant investment into the future of cleft research.

Study Design

Trialing the Collection and Storage of Biological Samples

To test the collection and storage of biological samples, a feasibility study was conducted at the South West Cleft Unit in Bristol. This included saliva samples in preservative for DNA extraction (Oragene, DNA Genotek) and blood samples (using EDTA blood tubes) from parents and infants, tissue samples from infants, and hair samples from parents. The cleft team recruited the target of 10 families very quickly and provided useful feedback on this process, which was incorporated into the main protocol. Biological samples were collected from the participants at either the presurgery meeting, at the lip/palate repair surgery, or the morning after the surgery. Tissue collected at surgery was preserved in two ways: in RNALater (Life Technologies, Glasgow, United Kingdom) for later RNA extraction and in tissue culture medium for immediate cell line production. DNA was obtained at sufficient quantity (>60 $\mu\text{g}/\text{sample}$) from all blood and parental saliva samples. Fibroblast cultures were established for all lip tissue samples (100% success rate) and a minority of the palate tissue samples (33% success rate). To measure the quality of the RNA from tissue, an RNA integrity number (RIN) score was produced; the RIN score must be >7 for RNA samples to be used in functional assays. The extracted RNA from tissue was of sufficient quality (RIN >7) and quantity (>20 $\mu\text{g}/\text{sample}$) to perform functional analyses. However, saliva samples from infants were not carried forward into the main study because of low DNA quantities (on average <5 $\mu\text{g}/\text{sample}$). Blood

samples from parents were also not included in the main study collection because of the high costs associated with employing phlebotomists at each site and the logistics of collecting samples from multiple sites. Hair collections in parents were successful but not included in the main study, as assessing toxin concentrations during early development is more easily achieved through analysis of blood samples collected from the children.

Overall, the feasibility study was considered extremely successful and demonstrated the possibility of collecting high-quality biological samples from both children and parents. It was concluded that for The Cleft Collective cohort studies, saliva would be collected from parents in preservative using Oragene kits (DNA Genotek, Ontario, Canada) for later DNA extraction. Child blood samples would be collected using EDTA as the anticoagulant of choice to preserve buffy coats for DNA extraction and plasma for biochemical, metabolomics, and environmental exposure measurements. Tissue would be collected from all children at surgery and stored in RNALater for later RNA extraction. Because of logistics and postal time delays, tissue would be collected in cell media only for immediate cell line production from the Bristol site.

Questionnaire Design

To ensure the content and design of the participant materials and questionnaires were also of high quality, a variety of questionnaires that have been used previously in similar research were systematically reviewed. Questions eliciting demographic, environmental, lifestyle, and psychological information of relevance to the cohort studies were identified and discussed further. Various experts in the applicable fields were asked to comment on the questionnaire content, including those associated with genetics, epidemiology, epigenetics, and clinical genetics. The different special interest groups (SIGs) for each discipline linked to CL/P services were also consulted. In particular, the psychology SIG played a crucial role in the rigorous selection of standardized psychology measures (Stock et al., in press-b). Questionnaires were produced as succinctly as possible to avoid creating an additional burden for participating families. Finally, all materials were reviewed by PPI representatives and adjusted in line with this feedback.

Research Questions

As a result of ongoing consultations with clinicians, researchers, and parents and thorough reviews of the existing literature, we identified three key research questions that parents are likely to ask following a diagnosis of cleft in their child: (1) What caused my child's cleft? (2) What are the best treatments for my child? (3) Will my child be OK, both now and in the

long term? To address these broad research questions, two parallel cohort studies were subsequently established; the Birth Cohort Study and the 5-Year-Old Cohort Study. The Birth Cohort Study will collect information as early as antenatal diagnosis, while the 5-Year-Old Cohort Study will collect data from the routine 5-year audit clinic onward.

Birth Cohort Study

Families are eligible to participate in the Birth Cohort Study if their child is diagnosed with CL/P within the recruitment period. In the interest of taking an inclusive approach to recruitment, families are eligible to participate regardless of the child's cleft type or the presence of any additional syndromes or conditions. Families are approached with information about the study by a specialist research nurse or a member of the cleft team, ahead of the child's primary surgical repair. Both the integration of the research nurse into the cleft team and the cleft team's established relationship with the family have been vital in supporting the recruitment process. Information packs include detailed participant information sheets, consent forms, questionnaires, and diagrams, which break down the research process into easy steps. Signed consent forms are then collected for each family member who wishes to participate. Consent from at least the biological mother and the child with CL/P is required; however, fathers/partners/guardians are also invited to participate, along with any biological siblings who are unaffected by CL/P. A saliva sample is then collected from both parents and siblings where applicable. From the child with CL/P, a blood sample and any discarded lip or palate tissue are collected at the time of surgery. A form describing the details of the surgery performed is completed by the surgeon, and each of the samples and documentation are given a unique barcode, which acts as an identifier for each individual participant. All biological samples are sent to the laboratory at the University of Bristol via post and are stored anonymously and securely. To create a sample resource that can be used to strengthen future research, samples are being stored in a biobank and are being processed into many small aliquots to prevent freeze-thawing and to maximize future use.

Parents are also asked to complete the questionnaires and to return them by post to the research team at the University of Bristol. As part of the consenting process, families are asked for their permission to extract relevant information from medical and educational records, as well as permission to link to national databases containing information about children born with CL/P, such as CRANE (www.crane-database.org.uk).

5-Year-Old Cohort Study

Families are eligible to participate in the 5-Year-Old Cohort Study if their child turns 5 during the recruitment period. As before, families are eligible regardless of the child's cleft type or the presence of any additional syndromes or conditions. Families are approached with information about the study prior to or at their child's 5-year audit clinic, by a specialist research nurse or a member of the cleft team. Consent forms and saliva samples are collected as before, and participants are asked to complete the questionnaires and return them to the research team. Again, families are asked for their permission to extract relevant information from medical and educational records and to link to applicable national databases.

Families are also eligible to participate in the 5-Year-Old Cohort Study if they were involved in a previous study titled "Cleft Care UK," which reviewed outcomes at age 5 in order to evaluate the centralization of cleft services in the United Kingdom. A wealth of information pertaining to these families has already been collected and therefore represents an opportunity for inclusion in the current cohort studies.

Implementation of the Cohort Studies

Ethical Approval

Research ethical approval was granted by the South West Central Bristol Ethics Committee. Global research and development (R&D) approval was given by University Hospitals Bristol (UHBristol). Local R&D approvals were subsequently obtained from each NHS Trust participating in the research. All ethical approvals and consents include permission to use samples in the future, to enable development of the data resource.

Support Costs

Following ethical approval, the cohort studies were adopted by the National Institute of Health Research (NIHR). This meant that participating cleft teams would be eligible for service support costs incurred as a result of the study being conducted. These support costs allowed for either a specialist research nurse to be employed to carry out recruitment or for existing members of the cleft team to allocate some of their time to the research study. The time and cost required for a research nurse were based on the feedback provided by the specialist nurse involved in the feasibility study in relation to the time taken to fully recruit each family and were calculated according to the support needs of each cleft team. This financial support has proved vital to the recruitment process.

Training the Cleft Teams

Before a cleft team can begin to recruit families into the cohort studies, members of each team must attend a 2-hour training session with the research team. The research team visits the cleft center to talk through the research protocol and to deliver all the necessary materials. The pragmatics of integrating the research study into the cleft team's existing program of work is also discussed.

Recruitment Targets

In total, the cohort studies aim to recruit up to 9800 individuals (mothers, fathers, affected children, and a limited number of unaffected siblings) from just more than 3000 families during the recruitment period. This figure is based on the number of children born with CL/P per year throughout the United Kingdom (approximately 1200 live births annually). Thus, the cohort studies aim to recruit a high percentage of children born during the 3.5-year recruitment period. The figure is capped at 9800 individuals, which is the maximum number of participants for whom NIHR support costs are available.

The Cleft Collective cohort studies have been recruiting since the end of August 2013. A staggered approach to the enrolment of cleft teams is being implemented. At the time of writing, 12 UK cleft teams were actively recruiting families into the cohort studies, with a further 2 teams engaged in the R&D process and 3 teams yet to become involved. All consecutive patients and their families are being invited to participate.

RESULTS

Achievements to Date and Future Ambitions

Current Recruitment Rates

Each cleft team has their own target recruitment figures, which reflect the number of patients they see each year and the level of service support each center receives. All enrolled teams are currently on target, just below their target, or exceeding their target, to meet their estimated figures by the end of the recruitment period. At the time of writing, 418 mothers, 308 fathers, 430 affected children, and 76 unaffected siblings are enrolled in the cohort studies (a total of 1232 individuals from 430 families). Eight hundred eighteen saliva samples from mothers, fathers, 5-year-old affected children, and unaffected siblings have been received (a current return rate of 86.3%), along with 237 blood samples and 226 tissue samples from affected children in the Birth Cohort (we are anticipating a 100% return

rate for these samples). Two hundred thirty-six questionnaires from mothers and 165 questionnaires from fathers have been received thus far (a current return rate of 55.2%). There is normally a delay between the family being enrolled in the study and the data being returned. If a family is enrolled in the study but their saliva samples and/or their questionnaires have not been received after 2 to 4 weeks, families are contacted by the research team to ensure they still want to participate in the study and to remind them to return their data.

Significantly fewer families are enrolled in the 5-Year-Old Cohort Study ($n = 146$) than are enrolled in the Birth Cohort Study ($n = 284$). This may be due to the number of contact points cleft teams have with families prior to the first surgery and/or related to the level of engagement from families in cleft treatment at different time points during the child's trajectory.

Public Engagement

Regular communication with stakeholders plays a vital role in the maintenance of any research program. The research team regularly updates The Cleft Collective website (www.cleftcollective.org.uk), as well as the Facebook (www.facebook.com/cleftcollective) and Twitter pages (@CleftCollective) with news stories and advertisements for related studies and events. The research team also produces twice-yearly newsletters, which are emailed to all key stakeholders, including PPI representatives and participants. Families are also encouraged to send in their photographs, which (with written consent) are used in participant and promotional materials, in presentations, and on The Cleft Collective website.

Substudies

Alongside the main cohort studies, the research team is also running a number of important substudies. This includes a large speech and language study, which is collecting data on speech assessments and recording verbal interactions between parents and infants. In addition, plans to conduct a novel 3D imaging study are under way. This study will capture 3D facial images from several members of the family and will help to better characterize the child and parent phenotype.

Within the general research field, the recent growth in the number of qualitative and mixed-methods studies has added to the richness of our understanding of individual experiences and has the potential to promote a more patient-centered focus in cleft research (Nelson et al., 2009; Rumsey and Stock, 2013). The Cleft Collective research team has been engaged in a number of complementary qualitative and quantitative studies, which have been extremely useful in informing the design of current and future studies within The Cleft

Collective research program (see Feragen et al., 2014; Feragen and Stock, 2014; Stock and Rumsey, in press; Norman et al., 2015; Stock et al., in press-a; Stock and Rumsey, 2015). For more information about The Cleft Collective substudies, please visit our website.

Antenatal Recruitment

Initially, families will be recruited into the cohort studies only after the child has been born. Once cleft teams are established and familiar with the research protocol, an antenatal recruitment arm will also be introduced. This will involve liaising with local maternity units and will allow for the collection of umbilical cord blood, more accurate environmental information during pregnancy, and analysis of the psychological impact of the antenatal diagnosis.

Challenges

As anticipated, the establishment of a national cohort study in CL/P has presented a range of significant challenges. First, the number and diversity of stakeholders (including the families, funders, NHS cleft teams and Trusts, Clinical Research Networks, charitable organizations, wider research community, and the research team itself) has resulted in competing needs, agendas, and priorities. Extensive and ongoing consultation and negotiation with each stakeholder is required, as is the need to be flexible and supportive. There is a need to identify common goals and invest in mutually beneficial working relationships. Second, the geographical spread of these stakeholders, including the 17 different surgical sites, has required the research team to travel long distances on a regular basis; however, face-to-face meetings are deemed to be essential. Third, the need to establish a UK-wide study and to secure the future funding of the cohort studies going forward is a normal and ongoing concern for all research projects. Fourth, the process of applying for global and local approvals has demonstrated the need to adapt applications to each committee's specifications; every NHS Trust operates differently, and one size does not fit all. The amount of time taken up by this aspect of the process should not be underestimated, however; taking a staggered approach to enrolling each cleft team into the study (as opposed to enrolling all cleft teams at once) has proven invaluable in terms of time and resource management. Fifth, obtaining service support costs for each cleft team has been vital to the facilitation of the research study. However, the process of obtaining this support differs vastly for each Clinical Research Network/NHS Trust and comes with its own challenges; for example, there is more support available in some Networks/Trusts than in others. Sixth, the challenges of recruiting non-English-speaking families, those with

functional illiteracy, those from different cultural and ethnic backgrounds, and those from lower income or socially disadvantaged groups are considerable. Support from the cleft teams to approach all eligible families, regardless of these demographic factors, has been crucial. The research team relies on the research nurses' and the cleft nurses' discretion in recruiting those who are able to provide fully informed consent. In cases in which this is deemed not to be possible, the research team is informed, and ways of overcoming these difficulties are discussed; for example, materials will be translated into the most commonly reported non-English language shortly. Seventh, deciding which constructs to measure, how to measure them, and at which time point represented a substantial challenge, which was overcome only through extensive collaboration with the SIGs and other expert groups from the beginning of the project. Finally, it is essential to understand the psychological impact of the condition and its treatment on families and be sensitive to this. Taking part in the research should not feel overwhelming or increase the burden families may already be experiencing. Engaging in PPI activities has supported the research team to overcome many of these difficulties and has been a crucial and educational experience. Our relationship with charitable organizations such as CLAPA has also been hugely valuable. As well as CLAPA helping to promote and support our research activities, we hope to provide CLAPA with a strong evidence base for their future work. We engage regularly with our PPI representatives, particularly if they are interested in participating in research but are not eligible to participate in the cohort studies themselves. For more information about the PPI principle adopted in these studies, please visit www.invo.org.uk.

The research team also anticipates a number of future challenges. Of primary importance is the need to secure additional funding to ensure the continuation of the cohort studies. We hope to follow the families who are enrolled in the cohort studies for as long as possible, in order to address important issues that arise throughout the patient journey as a whole. The ability to investigate developmental impacts and long-term outcomes for individuals with CL/P would also be of huge value to the field. A second future challenge will be to minimize loss to follow-up and thus reduce the risk of attrition bias. Again, PPI engagement will be vital to this effort. Third, locating and accessing appropriate control data will be challenging but also represents a significant opportunity for collaboration.

Opportunities

If successful, The Cleft Collective cohort studies will be home to one of the largest CL/P data banks in the world. Data will be collected consistently from a large

sample, across a range of disciplines and locations. The studies will collect longitudinal, prospective data from several members of the family, irrespective of diagnoses and demographic factors, and at key points along the child's developmental trajectory. This resource will place us in a unique and privileged position to address some of the biggest unanswered questions in CL/P research. The resource will be available to clinicians and researchers both within and outside of the United Kingdom for use with ethically approved projects and collaborations following an application to the research team. In addition, any data generated from samples will be returned to the research team to become part of the resource available to other researchers. Finally, all of the research findings will be shared with stakeholders, and teams will be supported to incorporate these findings into clinical practice around the world.

SUMMARY

The Cleft Collective cohort studies represent a significant step forward for research in the field of CL/P. Since the launch of the research program in 2012, research protocols have been developed and implemented within several UK cleft teams. Recruitment is currently on track to meet the ambitious target of approximately 9800 individuals from just more than 3000 families. In future years, the data collected will form a comprehensive resource of information about individuals with CL/P and their families. This resource will provide the basis for many future projects and collaborations both in the United Kingdom and across the world.

Acknowledgments. We are grateful to the families who have contributed to the development of this research and the families who are participating in our research. We are also grateful to the UK NHS cleft teams, The Healing Foundation, the Cleft Lip and Palate Association, and the West of England Clinical Research Network, who are helping to facilitate the studies.

REFERENCES

- Beaty TH, Murray JC, Marazita ML, Munger RG, Ruczinski I, Hetmanski JB, Liang KY, Wu T, Murray T, Fallin MD, et al. A genome-wide association study of cleft lip with and without cleft palate identifies risk variants near MAFB and ABCA4. *Nat Genet.* 2010;42:525–529.
- Beaty TH, Ruczinski I, Murray JC, Marazita ML, Munger RG, Hetmanski JB, Murray T, Redett RJ, Fallin MD, Liang KY, et al. Evidence for gene-environment interaction in a genome-wide study of nonsyndromic cleft palate. *Genet Epidemiol.* 2011;35:469–478.
- Birnbaum S, Ludwig KU, Reutter H, Herms S, Steffens M, Rubini M, Baluardo C, Ferrian M, Almedia de Assis N, Alblas MA, et al. Key susceptibility locus for nonsyndromic cleft lip with or without cleft palate on chromosome 8q24. *Nat Genet.* 2009;41:473–477.
- Danino A, Gradell J, Malka G, Moutel G, Herve C, Rosilio C. Social adjustment in French adults who had undergone standardised treatment of complete unilateral cleft lip and palate [in French]. *Ann Chir Plast Esthet.* 2005;50:202–205.
- Dixon MJ, Marazita ML, Beaty TH, Murray JC. Cleft lip and palate: understanding genetic and environmental influences. *Nat Rev Genet.* 2011;12:167–178.
- Feragen KJB, Stock NM. When there is more than a cleft: psychological adjustment when a cleft is associated with an additional condition. *Cleft Palate Craniofac J.* 2014;51:5–14.
- Feragen KJB, Stock NM, Rumsey N. Toward a reconsideration of inclusion and exclusion criteria in cleft lip and palate: implications for psychological research. *Cleft Palate Craniofac J.* 2014;51:569–578.
- Grant SF, Wang K, Zhang H, Glaberson W, Annaiah K, Kim CE, Bradfield JP, Glessner JT, Thomas KA, Garris M, et al. A genome-wide association study identifies a locus for nonsyndromic cleft lip with or without cleft palate on 8q24. *J Pediatr.* 2009;155:909–913.
- Hearst D. Can't they like me as I am? Psychological interventions for children and young people with congenital visible disfigurement. *Dev Neurorehabil.* 2007;10:105–112.
- Hunt O, Burden D, Hepper P, Johnston C. The psychosocial effects of cleft lip and palate: a systematic review. *Eur J Orthod.* 2005;27:274–285.
- Levin KA. Study design III: cross-sectional studies. *Evid Based Dent.* 2006;7:24–25.
- Long RE Jr, Hathaway R, Daskalogiannakis J, Mercado A, Russell K, Cohen M, Semb G, Shaw WC. The Americleft study: an inter-centre study of treatment outcomes for patients with unilateral cleft lip and palate. Part 1: principles and study design. *Cleft Palate Craniofac J.* 2011;48:239–243.
- Ludwig KU, Mangold E, Herms S, Nowak S, Reutter H, Paul A, Becker J, Herberz R, Chawa T, Nasser E, et al. Genome-wide meta-analyses of nonsyndromic cleft lip with or without cleft palate identify six new loci. *Nat Genet.* 2012;44:968–971.
- Mangold E, Ludwig KU, Birnbaum S, Baluardo C, Ferrian M, Herms S, Reutter H, Almeida de Assis NA, Chawa TA, Mattheisen M, et al. Genome-wide association study identifies two susceptibility loci for nonsyndromic cleft lip with or without cleft palate. *Nat Genet.* 2010;42:24–26.
- Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC. Cleft lip and palate. *Lancet.* 2009;374:1773–1785.
- Nelson PA, Glenny A-M, Kirk S, Caress A-L. Parents' experiences of caring for a child with a cleft lip and/or palate: a review of the literature. *Child Care Health Dev.* 2012;38:6–20.
- Noar JH. Questionnaire survey of attitudes and concerns of patients with cleft lip and palate and their parents. *Cleft Palate Craniofac J.* 1991;28:279–284.
- Norman A, Persson M, Stock NM, Rumsey N, Sandy J, Waylen A, Edwards Z, Hammond V, Partridge L, Ness A. The effectiveness of psychosocial intervention for individuals with cleft lip and/or palate. *Cleft Palate Craniofac J.* 2015;52:301–310.
- Persson M, Becker M, Svensson H. Academic achievement in individuals with cleft: a population-based register study. *Cleft Palate Craniofac J.* 2012;49:153–159.
- Petit-Zeman S, Cowan K. Patients/carers and clinicians can set joint priorities for research in cleft lip and palate. *Int J Pediatr Otorhinolaryngol.* 2013;77:309–310.
- Richman LC, McCoy TE, Conrad AL, Nopoulos PC. Neuropsychological, behavioral, and academic sequelae of cleft: early developmental, school age, and adolescent/young adult outcomes. *Cleft Palate Craniofac J.* 2012;49:387–396.
- Rumsey N, Stock NM. Living with a cleft: psychological challenges, support and intervention. In: Berkowitz S, ed. *Cleft Lip and Palate: Diagnosis and Management.* 3rd ed. Berlin: Springer-Verlag; 2013:907–917.
- Sandy J, Rumsey N, Persson M, Waylen A, Kilpatrick N, Ireland T, Ness A. Using service rationalisation to build a research network:

- lessons from the centralisation of UK services for children with cleft lip and palate. *Br Dent J.* 2012;212:553–555.
- Sandy J, Williams A, Mildinhal S, Murphy T, Bearn D, Shaw B, Sell D, Devlin B, Murray J. The Clinical Standards Advisory Group (CSAG) cleft lip and palate study. *Br J Orthod.* 1998;25:21–30.
- Shaw WC, Semb G, Nelson P, Brattstrom V, Molstead K, Prah Andersen B, Gundlach KK. The Eurocleft project 1996-2000: overview. *J Craniomaxillofac Surg.* 2001;29:131–140.
- Stanier P, Moore GE. Genetics of cleft lip and palate: syndromic genes contribute to the incidence of non-syndromic clefts. *Hum Mol Genet.* 2004;13:73–81.
- Stock NM, Feragen KJB, Rumsey N. Adults' narratives of growing up with a cleft lip and/or palate: factors associated with psychological distress and resilience. *Cleft Palate Craniofac J.* In press-a.
- Stock NM, Hammond V, Owen T, Kiff J, Shanly A, Rumsey N. Achieving consensus in the measurement of psychological adjustment to cleft lip and/or palate. *Cleft Palate Craniofac J.* In press-b.
- Stock NM, Rumsey N. Starting a family: the experience of parents with cleft lip and/or palate. *Cleft Palate Craniofac J.* In press.
- Stock NM, Rumsey N. Parenting a child with a cleft: the father's perspective. *Cleft Palate Craniofac J.* 2015;52:31–43.
- Williams L, Dures E, Waylen A, Ireland T, Rumsey N, Sandy J. Approaching parents to take part in a cleft gene bank: a qualitative pilot study. *Cleft Palate Craniofac J.* 2012;49:425–436.
- Wu T, Liang KY, Hetmanski JB, Ruczinski I, Fallin MD, Ingersoll RG, Wang H, Huang S, Ye X, Wu-Chou YH, et al. Evidence of gene-environment interaction for the IRF6 gene and maternal multivitamin supplementation in controlling the risk of cleft lip with/without cleft palate. *Hum Genet.* 2010;128:401–410.